

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
USA

August 26, 1999
HeSk/NSH

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Novo Nordisk



Novo Nordisk A/S

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A/S Reg. No. 16201

[Docket No. 99D-1454]

Gentlemen:

**Draft Guidance for Industry on Nasal Spray and inhalation Solution,
Suspension, and Spray Drug Products; Chemistry, Manufacturing,
and Controls Documentation**

Novo Nordisk A/S has reviewed the above draft and would like to comment
as follows.

Lines 372-373

We suggest that the sentence "Chromatographic retention time alone is not
an adequate method to ensure the identity of the drug substance in the
drug product" be changed to "If a chromatographic method is used, the
method should be sufficiently specific to properly verify the identity of the
drug substance by the retention time." An example of such a method is the
pharmacopoeial identity test of human, bovine or porcine insulin in insulin
drug products.

Lines 388-395

We suggest the nomenclature in this section be changed. According to the
ICH guideline, Topic Q6B "Specifications: Test procedure+ and Acceptance
Criteria for **Biotechnological/Biological** Products"; **impurities** and
degradation products should be classified as "Process-related impurities",
"Product related impurities" or "Product related substances".

Lines 397-402

The requirement for stabilizing excipient(s) assay seems too stringent and
we suggest the following approach:

The use of stabilizing excipients should be justified and documented during
investigational studies, so that a specific assay on the finished drug

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product specification may be unnecessary. Such documentation may include data on the content of excipient during investigational studies to demonstrate there is no significant loss to primary **packaging** material (from neither excipient nor the active drug substance), proper process validation data showing consistent content of excipient at release within defined acceptance criteria, and **cGMP** documentation **of the** manufacturing process.

Lines 812-815

The requirement in the following sentence seems too stringent: "For device-metered nasal or inhalation spray drug products designed for use with replaceable reservoirs, the device should be specific for the intended formulation reservoir only and should not allow use of an alternate reservoir that contains a different formulation." We suggest that the sentence be supplemented by the following: "If a device can be used with different formulation reservoirs (e.g., different potencies of a drug substance), it must include a feature clearly indicating the formulation contained in the reservoir."

Lines 1057-1 062

As some drug products require cold storage, we suggest that test storage conditions include requirements for temperature and humidity for cold storage.

We suggest the lines are changed to the following: "For drug products packaged in semipermeable containers (e.g., low density polyethylene) without protective packaging, the above test storage conditions should be replaced with the following conditions:

Storage under controlled temperature: (1) accelerated ($40\pm 2^{\circ}\text{C}/15\pm 5\%\text{RH}$), (2) intermediate ($30\pm 2^{\circ}\text{C}/40\pm 5\%\text{RH}$), if applicable, and (3) long-term ($25\pm 2^{\circ}\text{C}/40\pm 5\%\text{RH}$).

Storage under refrigerated conditions: 1) accelerated ($25\pm 2^{\circ}\text{C}/40\pm 5\%\text{RH}$), (2) long-term ($5\pm 3^{\circ}\text{C}$ /no specific limits for humidity).

Line 1121

The requirement for **setting** the expiration dating period based on full shelf-life stability studies does not appear to be in accordance with the

requirement in the ICH Q1A Stability Guideline for 12 months' stability data at submission.

Sincerely,

Helle Skov

Helle Skov
MSc (pharm), PhD
Health Care Quality
QA Insulin Coordination

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(Docket No. 99D-1454)



Novo Nordisk

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Prioritaire





Shipment Airwaybill

(Non negotiable)

7051672443

Quote this shipment number in an enquiry

ORIGIN COUNTRY	DESTINATION
6	1

From (Sender)

Account no. 302080304

Sender's name

Helle Skov (Ms)

Sender's reference first twelve characters will be shown on invoice

240/5859900/HeSk
NOVO NORDISK A/S

HEALTH CARE
NOVO ALLE
2880 BAGSVARD DENMARK

Postcode 2880 KEY

Phone / Fax / Telex

44 44 88 88

To (Receiver)

Food and Drug Administration

Dockets Management Branch (HFA-305)
5630 Fishers Lane, rm. 1061
Rockville

Postcode MD 20852

USA

Contact person

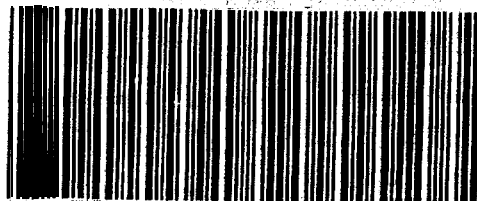
Phone / Fax / Telex

Sender's authorisation and signature

We agree that DHL's standard terms apply to this shipment and limit DHL's liability in Warsaw Convention may also apply (see reverse).
We understand that DHL does not transport cash or dangerous goods (see reverse).

Signature Nancy Spang-Stanssen
for Helle Skov

Date 30/08/99



3 Shipment details

Not all payment and service options are available in all countries.

Services

- ☒ DOCUMENT
- ☐ WORLDWIDE PARCEL EXPRESS all declarables
- ☐ INTRA EC (in free circulation)
- ☐ EXPRESS DOCUMENT
- ☐ DOMESTIC
- ☐ WORLDMAIL Airmail/Printed Matter specify one
- ☐ OTHER SERVICE specify

Transport charges

- If left blank sender pays transport charges
- ☐ Sender
- ☐ Cash / Cheque / Credit Card For approved customers only
- ☐ External Billing Agreement
- ☐ Transport Collect

Shipment Insurance see reverse

☐ YES

Full description of contents

International Worldwide Parcel Express shipments only

Declared value give currency

Sender's VAT / GST no.

Harmonised commodity code if applies

Receiver's VAT / GST no. or EIN / SSN

Type of export

☐ PERMANENT ☐ REPAIR/RETURN ☐ TEMPORARY

Destination duties / taxes If left blank receiver pays duties / taxes

☐ Receiver ☐ Sender ☐ Other Specify destination approved account number

4 Size and weight

No. of pieces 1 Weight 0.5 kg

Dimensions cm L x W x H

VOLUMETRIC/CHARGED WEIGHT

CODES

CHARGES services

Special

Insurance

Other / VAT

CURRENCY CODE

TOTAL

TRANSPORT COLLECT STICKER No.

PICKED UP BY

Route No. 1202

Time

Date 30/8

Parcel copy